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The Patent Office
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1. Your reference — JPP

2. Patent application number *(The Patent Office will fill in this part)* — 9919673.5 — 20 AUG 1999

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

CANCER RESEARCH CAMPAIGN TECHNOLOGY LIMITED
Cambridge House
6-10 Cambridge Terrace
LONDON
NW1 4JL

Patents ADP number *(if you know it)* 39841500 02

If the applicant is a corporate body, give the country/state of its incorporation — United Kingdom

4. Title of the invention

2-ARYLBENZAZOLE COMPOUNDS

5. Name of your agent *(if you have one)*

WILSON GUNN SKERRETT

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

Charles House
148/9 Great Charles Street
Birmingham B3 3HT

Patents ADP number *(if you know it)* 7710734001

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
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Patents Form 1/77

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Continuation sheets of this form	
Description	35
Claim(s)	14
Abstract	
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Priority documents	
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Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
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11. I/We request the grant of a patent on the basis of this application.

Signature: Wilson, Gunn, Herrett

Date: 19 August 1999

12. Name and daytime telephone number of person to contact in the United Kingdom

Mr J P PEEL
0121-236-1038

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2-ARYLBENZAZOLE COMPOUNDS

Field of the Invention

The present invention relates to certain novel benzazole compounds, specifically 2-arylbenzazole compounds, and compositions thereof which are biologically active in that they are able selectively to inhibit proliferation of certain mammalian tumor cells.

Background and Summary of the Invention

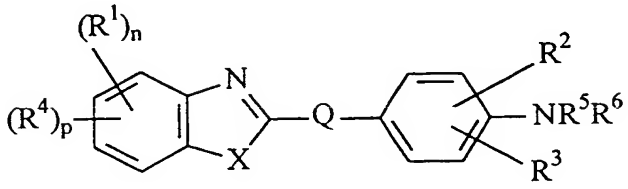
Various 2-arylbenzazole compounds found to be active in inhibiting proliferation of certain tumor cells and exemplified by 2-(4'-aminophenyl)benzothiazole and close analogues or acid addition salts thereof are disclosed in PCT international patent publications WO 95/06469 and WO 96/26932.

For some of the benzazole compounds disclosed in WO 95/06469, for instance the compound 2-(4'-aminophenyl)benzothiazole which has been designated the reference code CJM 126, a remarkably high specific inhibitory activity has been found in respect of certain human breast cancer cell lines. In WO 96/26932 compounds were disclosed that exhibit anti-proliferative activity selectively in respect of a number of different cell lines that relate to a range of various mammalian cancers other than human breast cancer.

It has now been found that by modifying the structure of the prior art compounds, their activity can be improved, whilst retaining the selectivity.

The compounds with which the present invention is concerned are also 2-arylbenzazole compounds which are believed to comprise novel or new chemical entities and which are of particular interest as active chemotherapeutic agents for use in therapy, especially antitumor therapy, by virtue of an ability to inhibit proliferation of certain tumor cells.

According to the invention there is provided a compound of formula



(I)

characterised in that

X represents S or O;

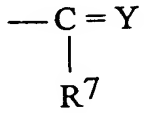
R^1 represents alkyl, hydroxyl, alkoxy or aralkoxy;

R^2 represents hydrogen, NO_2, N_3, halogen, alkyl, CN, CF_3, cycloalkyl, or a substituted alkyl oxysulphonyl group;

R^3 represents hydrogen, halogen, alkyl, NO_2, N_3, Pyrrolidino, Piperidino or Morpholino;

R^4 represents F and/or CF_3;

R^5 and R^6 each independently represent hydrogen, $SO_3^-M^+$ (wherein M^+ is a monovalent cation or cationic group), an amino acid, an alkyl, an acyl or benzoyl group



wherein Y represents O or S, and R^7 represents alkyl (including cyclo-alkyl), $-CH(R^8)NH_2$, a halogenated alkyl, or phenyl and R^8 represents hydrogen, alkyl-S-alkyl, alkylphenyl, alkylphenol, optionally substituted alkyl or alkyl-heterocyclyl;

Q represents a direct bond, $-CH_2-$ or –CH=CH-;

n represents zero, 1 or 2; and

p represents zero, 1, 2 or 3;

or a prodrug and/or a pharmaceutically acceptable salt thereof;

subject to the following provisos:

(a) an alkyl group when present as such in the compound or as a moiety in group such as alkoxy is composed of less than 6 carbon atoms and, where it is not cycloalkyl, the alkyl chain is optionally branched;

(b) n represents zero or 1 when p represents 3;

(c) when p represents zero, R^5 or R^6 represents $-C(Y)-CH(R^8)NH_2$;

(d) where a group is optionally substituted, a substituent is selected from halogen, OH, SH, NH_2, COOH and $CONH_2$;

(e) a heterocyclyl group when present as such or as a moiety in a group comprises from 3 to 9 carbon atoms and 1, 2 or 3 heteroatoms selected from O, S and N, the group or moiety is optionally in the form of fused rings.

R^4 preferably represents F. p preferably represents 1 or 2. Preferably when one of R^5 and R^6 represents $-C(Y)-CH(R^8)NH_2$, the other represents hydrogen.

Preferred compounds of formula (I) wherein n represents 1 include compounds in which R^1 represents alkyl, alkoxy or benzyloxy. It is also usually preferred that X represents sulphur. Preferred compounds of formula (I) may also be further characterised by at least one of the following features:

(a) at least some alkyl groups when present as such or as a moiety in other groups such as alkoxy are methyl or ethyl;

(b) where a substituent represents halogen or is substituted by halogen, it or the halogen substituent is selected from fluorine, iodine, bromine and chlorine.

A suitable prodrug of a compound of formula (I) is an amino acid amide. Thus R^5 or R^6 optionally represents $-C(O)-CH(R^8)NH_2$. Examples of suitable

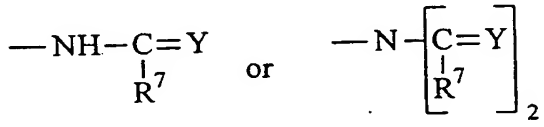
substituents for R^8 to represent include hydrogen, $-CH_3$, $-(CH_2)_4NH_2$, $-CH_2OH$, $-CH_2CH(CH_3)_2$ or $-CH_2(C_6H_5)$. The stereochemistry of the R^5 or R^6 substituent is either D or L or it is a racemic mixture. The L-stereoisomer is preferred. R^8 preferably represents CH_3, $-(CH_2)_4NH_2$ or CH_2OH.

It has been found that at least for compounds of formula (I) wherein R^5 and R^6 both represent hydrogen, i.e. wherein the phenyl group has a 4'-NH_2 substituent, a very effective degree of anti-proliferative activity against various mammalian tumor cells may arise when R^2 represents a halogen atom, or represents an lower alkyl group (preferably Me or Et), in the 3' position of the phenyl group. For example, the particular combinations of 4'-NH_2 and 3'-F, 4'-NH_2 and 3'-Cl, 4'-NH_2 and 3'-Br, 4'-NH_2 and 3'-I, 4'-NH_2 and 3'-Me, and 4'-NH_2 and 3'-Et in the phenyl group of the 2-aryl component have been found to yield compounds with potent anti-proliferative properties against at least some selected tumor cells. The 3' position substituent may alternatively be substituted by a cyano group, giving a further combination 4'-NH_2 and 3'-CN.

Compounds of formula (I) wherein R^2 is a 3'-substituent in the phenyl group, and which are of particular interest, include those compounds where n represents zero and R^5 and R^6 are both hydrogen and the combination of substituents R^3, X and R^2 is selected from one of the following combinations:

R^3	X	R^2
H	S	3'-Me
H	S	3'-Et
H	O	3'-I
H	S	3'-Br
H	S	3'-Cl
H	S	3'-CN
5'-Br	S	3'-Br
5'-Cl	S	3'-Cl
5'-Me	S	3'-Cl
H	S	3'-F

Another group of benzazole compounds which provide some very promising anti-proliferative agents for use in antitumor therapy are compounds of formula (I) wherein the substituent NR^5R^6 is an N-acyl or N-diacyl derivative (or equivalent benzoyl derivative), e.g.



wherein, as hereinbefore specified, Y represents O or S and R^7 represents alkyl (including cycloalkyl such as cyclobutyl), $-CH(R^8)NH_2$, a halogenated alkyl or phenyl.

Acyl or benzoyl derivatives as referred to above which are of particular interest include those compounds where NR^5R^6 is an N-acyl group (or N-benzoyl group) and where the combination of substituents X, R^2, Y and R^7 is selected from one of the following combinations.

X	R^2	Y	R^7
S	H	O	Me
O	H	O	Me
S	H	S	Me
O	H	S	Me
S	H	O	CH_2Cl
O	H	O	CH_2Cl
O	3'-I	O	CH_2Cl
O	3'-NO_2	O	Me
S	H	O	$CHCl_2$
S	H	O	Ph
S	H	O	Cyclobutyl

Particular preferred compounds of formula (I) are those wherein n represents zero, X represents S, R^3, R^5 and R^6 represent H, Q represents a direct bond and p, R^4 and R^2 represent one of the following combinations:

p	R^4	R^2	Compound of formula
1	4-F	3-CH_3	(Ia)
1	6-F	3-CH_3	(Ib)
1	4-F	H	(Ic)
1	6-F	H	(Id)
2	4,5-diF	3-CH_3	(Ie)
2	4,6-diF	3-CH_3	(If)
2	5,7-diF	3-CH_3	(Ig)
1	7-F	3-CH_3	(Ih)
2	5,6-diF	3-CH_3	(Ii)
2	6,7-diF	3-CH_3	(Ij)
1	5-F	3-CH_3	(Ik)
1	5-F	H	(Il)
1	4-F	3-I	(Im)
1	5-F	3-I	(In)
1	6-F	3-I	(Io)
1	4-F	3-Cl	(Ip)
1	5-F	3-Cl	(Iq)
1	6-F	3-Cl	(Ir)
1	4-F	3-Br	(Is)
1	5-F	3-Br	(It)
1	6-F	3-Br	(Iu)

A further particularly preferred compound of formula (I) is a compound of formula (I) wherein n represents zero, X represents S, Q represents a direct bond, one of R^5 and R^6 represents H and the other represents $-C(Y)R^7$ wherein Y represents O and R^7 represents $-CH(R^8)NH_2$, R^3 represents H, and p, R^4, R^2 and R^8 represent one of the following combinations.

p	R^4	R^2	R^8	Compound of formula
Zero	-	H	$-CH_3$	(Iv)
Zero	-	3-CH_3	$-CH_3$	(Iw)
Zero	-	3-Cl	$-CH_3$	(Ix)
Zero	-	H	$-(CH_2)_4NH_2$	(Iy)
Zero	-	3-CH_3	$-(CH_2)_4NH_2$	(Iz)
Zero	-	3-Cl	$-(CH_2)_4NH_2$	(Iaa)
Zero	-	3-CH_3	$-CH_2OH$	(Iab)
1	6-F	3-CH_3	$-CH_3$	(Iac)
1	5-F	3-CH_3	$-(CH_2)_4NH_2$	(Iad)
1	6-F	3-CH_3	$-(CH_2)_4NH_2$	(Iae)
1	5-F	3-CH_3	$-CH_3$	(Iaf)
1	5-F	3-CH_3	$(CH_3)_2CHCH_2$	(Iag)
1	5-F	3-CH_3	$(C_6H_5)CH_2$	(Iah)
1	5-F	3-CH_3	H	(Iai)

It will also be understood that many of the compounds in accordance with the invention may be in the form of pharmaceutically acceptable salts, especially acid addition salts derived from an acid selected for example from the group comprising: hydrochloric, hydrobromic, sulphuric, nitric, phosphoric, maleic, salicylic, p-toluenesulphonic, tartaric, citric, lactobionic, formic, malonic, panto-thenic, succinic, naphthalene-2-sulphonic, benzene-sulphonic, methanesulphonic and ethanesulphonic.

It should also be understood, however, that where reference is made in this specification to compounds of formula (I) such reference should be construed as extending not only to their pharmaceutically acceptable salts but also to other pharmaceutically acceptable bioprecursors (pro-drug forms) where relevant. Moreover, where any of the compounds referred to can exist in more

than one enantiomeric form or atoms have more than one isotope, all such forms or isotopic compounds, mixtures thereof, and their preparation and uses are within the scope of the invention. The ^{18}F-substituted compounds of the invention are of use for imaging purposes.

More particularly, sulphamate salts constituting potential water-soluble pro-drug forms of the 2-(aminophenyl)benzazole compounds previously mentioned, especially 4'-NH_2 derivatives, provide a further category of promising benzazole compounds within the scope of the present invention. These sulphamate salts may break down in biological systems to form corresponding amines, and will generally be compounds of formula (I) wherein NR^5R^6 is 4-$NHSO_3^-M^+$ as hereinbefore defined. In preferred embodiments M^+ represents an alkali metal cation such as Na^+ or represents a cationic group such as NH_4^+.

Like acyl derivatives such as N-acetyl and N-chloro-acetyl derivatives, and like other acid addition salts, e.g. hydrochloride, dihydrochloride, methanesulphonic acid and ethanesulphonic acid addition salts, these sulphamate salts are expected to be equally effective in inhibiting proliferation of tumor cells in antitumor therapy as the parent amino compounds from which they may be considered to be derived. The salts may of course dissociate in water or other aqueous media to provide the active antitumor compound, and in practice these water soluble compounds are likely to be the most preferred compounds for making up acceptable pharmaceutical formulations.

Specific sulphamate salts of compounds of formula (I) which are of particular interest include compounds in which the combination of substituents X, R^2 and NR^5R^6 is selected from the following combinations:

X	R^2	NR^5R^6
S	H	$NHSO_3^-Na^+$
S	H	$NHSO_3^-NH_4^+$
O	H	$NHSO_3^-Na^+$
S	3-I	$NHSO_3^-Na^+$
S	3-Me	$NHSO_3^-Na^+$

The invention also comprises the use of a 2-arylbenzazole compound as specified above for therapy, especially for making a medicament or pharmaceutical composition for selective use in antitumor therapy.

As hereinafter described, the invention also includes pharmaceutical compositions or preparations, conveniently in unit dosage form, for selective use in antitumor therapy, said compositions or preparations comprising as the active substance a compound of formula (I).

Biological results

In vitro cytotoxicities

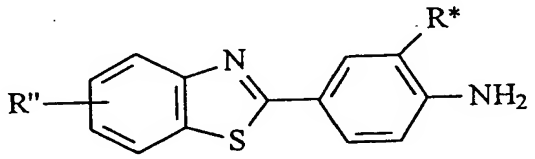
In carrying out the following cytotoxicity assays, the method used corresponded to that disclosed in the example on pages 9 and 10 of WO 96/26932. It has surprisingly been found that many of the compounds of formula (I) are highly potent, inhibiting 50% cell growth at < 10 nM (Table 1).

TABLE 1

	IC_{50} (nM)			
R"	II(R*=H)	II(R*=I)	II(R*=Me)	II(R*=Br)	II(R*=Cl)
MCF-7					
4-F	8.54	7.88	<0.10	38.2	0.95
5-F	<0.10	<0.10	<0.10	<0.10	7.09
6-F	<0.10	<0.10	<0.10	45.5	4.08
MDA 468					
4-F	29.4	9.11	0.13	24.0	1.93
5-F	<0.10	<0.10	<0.10	0.20	18.9
6-F	48.1	<0.10	0.11	68.7	11.7

IC_{50} values were determined by 3-day MTT assays (n=8).

wherein the compounds used were compounds of formula



(II)

wherein R* represents H, CH_3, Cl, Br or I and R" represents F.

The selectivity of antitumor effect of the compounds of the invention is identical to the prior art compounds disclosed in WO 96/26932, with activity observed in the same cell lines that were growth inhibited by their respective non-fluorinated parent compounds, eg, breast MCF-7 and MDA 468 cells. Prostate PC 3 and non-malignant breast HBL 100 cells were unresponsive to the compounds of the invention.

A problem with the prior art compounds is that they are characterised by a biphasic dose-response relationship in the sensitive cell lines only: cell kill occurs at low nanomolar concentrations of the compounds, followed by a proliferative response at low micromolar concentrations (termed the "second growth phase"). It has surprisingly been found that the biphasic response is

eliminated in the compounds of the invention for which R^4 does not represent 6-F.

In addition to breast (MCF-7, T-47D), ovarian (IGROV 1, OVCAR 3), and renal (TK 10) cell lines, the compounds of the invention wherein R^4 is 5-F were active against colon (HCC 2998) cell lines in the standard 2 day sulforhodamine B assay - these colon cell lines respond to the non-fluorinated prior art compounds only after prolonged 6 day exposures.

Further *in vitro* data is given in Table 2.

TABLE 2

Mean IC_{50} values (nM)

Compound of Formula	MCF-7	MDA 468
(Iw)	360	340
(Iz)	80	70
(Iad)	40	158
(Iae)	367	320
(Iac)	44	297
(Ie)	0.64	0.59
(If)	<0.30	6.97
(Ig)	0.90	4.22
(Ih)	2.39	-
(Ii)	<0.1	-

IC_{50} values were determined by 3-day MTT assays (n=8).

Among the prodrugs, 2-(4-amino-3-methylphenyl)-5-fluorobenzothiazole alanine (Iaf) shows outstanding antitumour potency, with IC_{50} in MCF-7 cells > 5 fold lower than that of other amido prodrugs. None of these prodrugs elicits the biphasic dose-response.

NCI mean graphs of the amino acid salts are identical to those of their respective parent compound, with selective antitumour activity against certain ovarian (OVCAR-5), renal (TK-10) and breast (MCF-7, T-47D) cell lines.

In vivo xenograft studies

The compounds of formula (Ib) and (Ik) were evaluated for *in vivo* antitumor property in ER positive MCF-7 and ER negative MT-1 human breast tumor xenografts implanted in nude mice using the experiment details described at pages 11 and 12 of WO 96/26932. Significant growth inhibition of MCF-7 xenografts was observed with both compounds given i.p., with the compound of formula (Ik) being toxic at 12.5 mg/kg. In the MT-1 xenografts, the compound of formula (Ik) was toxic at 25 mg/kg; at the lower dose of 12.5 mg/kg, the compound of formula (Ib) produced more pronounced growth inhibition than did the same dose of the compound of formula (Ik) although both analogues caused dose-dependent tumor growth inhibition and weight loss. Blood parameters (white blood cell and platelet counts) and the level of liver transaminases were not adversely affected by either compound.

The *in vitro* growth inhibitory property of the compounds of formula (Iw) and (Iz) is paralleled by significant *in vivo* growth retardation of human breast tumour xenografts (ER positive MCF-7 and ER negative MT-1) implanted in nude mice. At a dose of 12.5 mg/kg (given i.v.), the alanyl-prodrug of formula (Iw) caused a greater extent of growth retardation than its lysyl- counterpart of formula (Iz) against MCF-7 xenografts. Dose-dependent body weight loss was observed with the compound of formula (Iz). In the MT-1 xenografts, the compound of formula (Iw) was toxic at 25 mg/kg, while the compound of formula (Iz) was toxic at both doses of 12.5 mg/kg and 25 mg/kg; moderate tumor growth inhibition was observed in surviving mice treated with either prodrug.

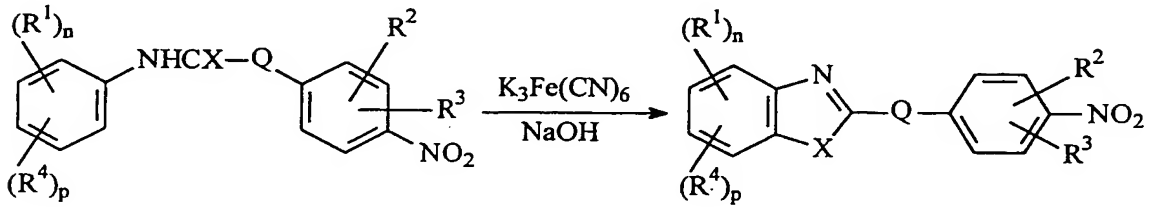
Pharmacokinetic studies

Although the compounds of formula (Iw) and (Iz) were stable in rat plasma *in vitro*, it was surprisingly found that both prodrugs were readily removed from plasma and reconverted to their parent compound when either compound was given to rats intravenously (i.v.) at 25 mg/kg.

Preparative Methods

In most cases the compounds of formula (I) of the present invention can readily be synthesised by various routes from easily available starting materials. By way of example, several such general synthetic routes, designated Route A, Route B, Route C, Route D and Route E are described as follows (the substituents for the starting materials and products of these synthetic routes have the meanings given above in connection with the definition of the compound of general formula (I) unless otherwise stated):

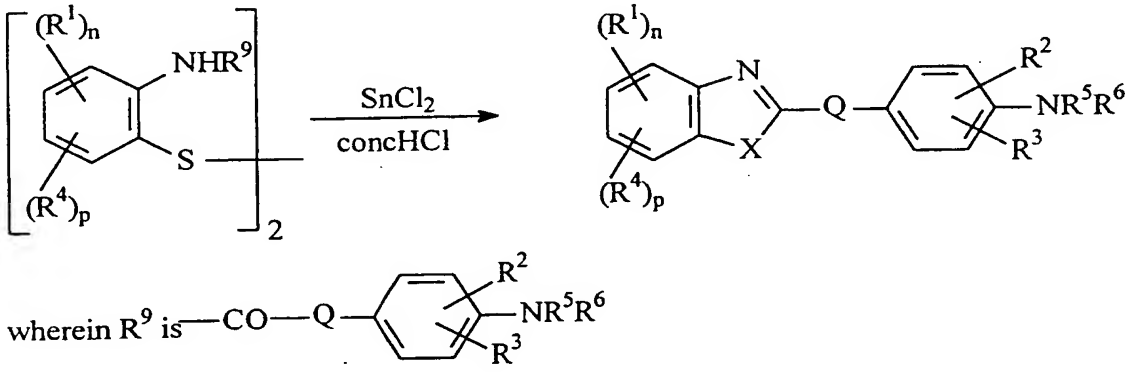
Route A



In the general method for Route A, in a typical procedure the appropriate substituted benzanilide (1 Mol. equiv.) is finely powdered and mixed with a little ethanol to form a wet paste. A 30% w/v solution of aqueous sodium hydroxide (8 Mol. equiv.) is added and diluted with water to form a suspension/solution of the benzanilide in 10% w/v aqueous sodium hydroxide. Aliquots of this suspension/solution are then introduced dropwise at one minute

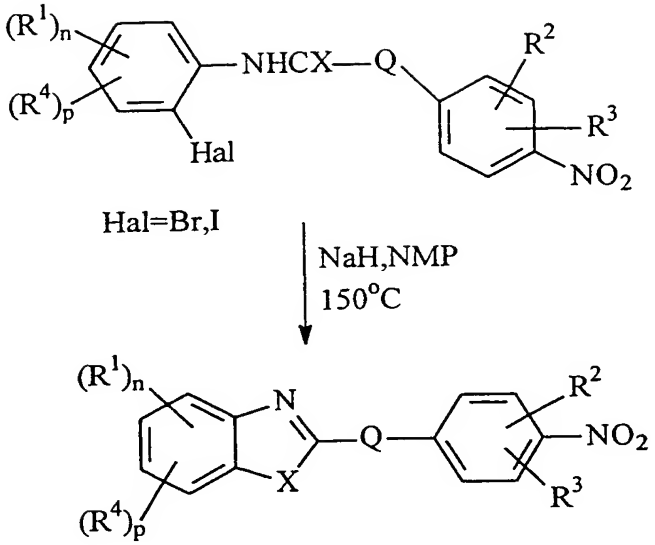
intervals into a stirred solution of potassium ferricyanide (4 Mol. equiv.) in water at 80-90°C. The reaction mixture is heated for a further 30 minutes, then cooled. The product is collected, washed with water and crystallised. Further reduction yields a compound of formula (I) wherein R^5 and R^6 each represent hydrogen. Methods well known in the art may be used to prepare further compounds of formula (I) where R^5 and/or R^6 do not represent hydrogen.

Route B



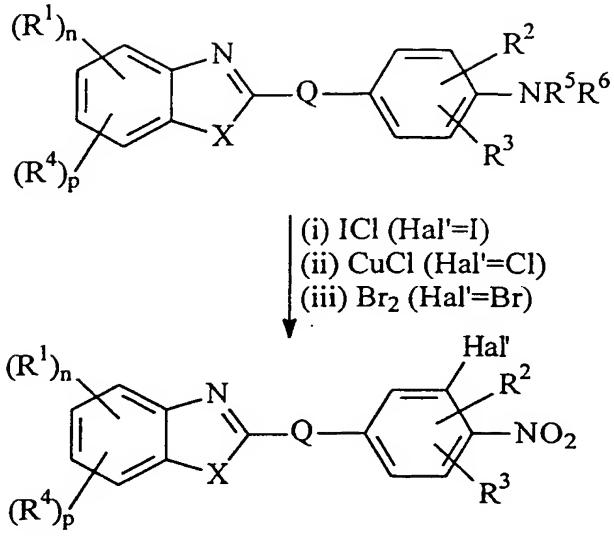
In the general method for Route B, typically the starting material is added with tin (II) chloride to a solution of conc HCl, ethanol and water. The reaction mixture is heated under reflux for 15 hours, cooled to 25°C and poured into water. Sodium hydroxide is added slowly, and the mixture stirred for 60 minutes. The precipitate is filtered from solution, and washed with water to leave a solid which is purified by column chromatography (dichloromethane) followed by recrystallisation from ethanol to give clear needles.

Route C



In the general method for Route C, sodium hydride (1.1 mol. equiv) is slowly added to a solution of starting material (1.0 mol. equiv) in N-methyl-2-pyrrolidinone (NMP) at room temperature with stirring. The mixture is heated at 150°C for one hour then allowed to cool. Water (50ml) is then added and the precipitate collected by filtration and dried *in vacuo* to give the solid product. Reduction yields a compound of formula (I) wherein R^5 and R^6 each represent hydrogen. Methods well known in the art may be used to prepared further compounds of formula (I) where R^5 and/or R^6 do not represent hydrogen.

Route D



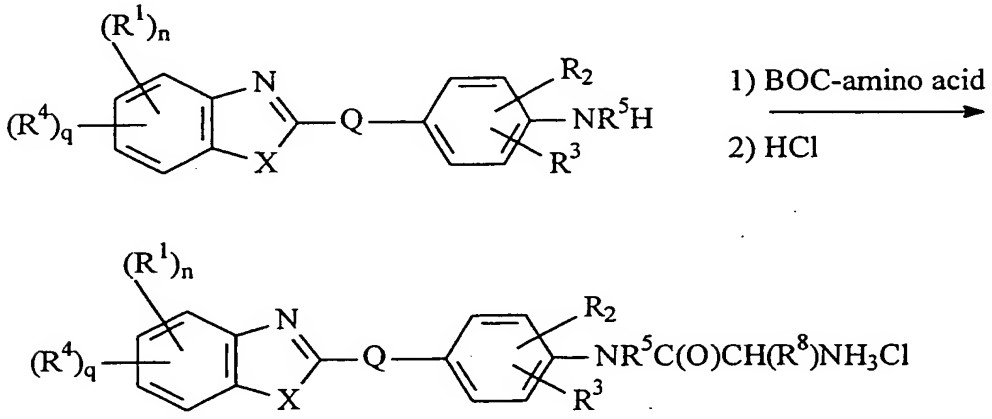
Route D is for 3'-halogenation of compounds of formula (I). The general methods for each variant are as follows:

(i) in the general method for iodination, ICl is added to a solution of the starting material in acetic acid at 25°C. The resulting solution is stirred for 2 hours, then the solvent is removed under vacuum. The residue is dissolved in chloroform and washed with aqueous sodium carbonate, aqueous sodium thiosulfate and water. Evaporation of the solvent, is followed by column chromatography (chloroform) and recrystallisation from methanol giving needles.

(ii) in the general method for chlorination, a solution of the starting material and copper(I) chloride in DMF is heated under reflux overnight. After cooling, the reaction mixture is poured into ethyl acetate, the precipitated solids are filtered off and the resulting solution evaporated to dryness. The product is purified by column chromatography (dichloromethane) followed by recrystallization from methanol to give a pale green solid.

(iii) in the general method for bromination, bromine is added to a solution of the starting material in dichloromethane at 10°C. The resulting solution is stirred for 10 min, then poured into water/ice. The organic layer is removed and washed with 10% sodium thiosulfate, water and evaporated. The product is purified by column chromatography (dichloromethane) to leave a white solid.

Route E



A compound of formula (I) wherein R^6 represents hydrogen (7.75mmol) is dissolved in dichloromethane (100ml) and stirred at room temperature. To this solution is added 1-ethyl-3-(3'-dimethylaminopropyl)-carbodiimide hydrochloride (2.3mmol), HOBt (2.3mmol) and the appropriate BOC protected amino acid (2.3mmol). This procedure is repeated and the reaction is continued until a clear solution is obtained. The solvent is removed under vacuum and the resulting oil purified by column chromatography (2% methanol/dichloromethane). Recrystallisation from ethanol gives a white solid.

The BOC protected amino acid derivative thus obtained (3.5mmol) is dissolved in dichloromethane (20ml). Dry HCl gas is bubbled through the solution to saturate it, then the reaction mixture is stirred for a further 2 hrs at 25°C. The precipitate is filtered from solution and washed with

dichloromethane (10ml), to leave a bright yellow crystalline solid. Recrystallisation, if required, is carried out using methanol/acetone.

Therapeutic Use

As already indicated, compounds of this invention have been found to inhibit tumor cell proliferation and to have significant selective antitumor activity. Antitumor activity may be evidenced by reduction of tumor cell number in mammals bearing cancer tumors, e.g. breast cancer tumors, and a consequent increase in survival time as compared to a control provided by animals which are untreated. Antitumor activity is further evidenced by measurable reduction in the size of solid tumors following treatment with the compounds of this invention compared to the tumors of untreated control animals.

Accordingly, as previously stated the compounds of the present invention are of particular interest for the treatment of a range of selected cancer tumors, and the invention further provides a method for the treatment of a patient suffering from certain kinds of cancer. For this purpose, an effective non-toxic amount of a compound of formula (I) as hereinbefore defined, may be suitably administered, orally, parenterally (including subcutaneously, intramuscularly and intra-venously), or topically. The administration will generally be carried out repetitively at intervals, for example once or several times a day.

The amount of the compound of formula (I) which is required in order to be effective as an antitumor agent for treating mammals will of course vary and is ultimately at the discretion of the medical or veterinary practitioner treating the mammal in each particular case. The factors to be considered by such a practitioner, e.g. a physician, include the route of administration and pharmaceutical formulation; the mammal's body weight, surface area, age and general condition; and the chemical form of the compound to be administered.

However, a suitable effective antitumor dose may be in the range of about 1.0 to about 75 mg/kg bodyweight, preferably in the range of about 5 to 40mg/kg with most suitable doses being for example in the range of 10 to 30mg/kg. In daily treatment for example, the total daily dose may be given as a single dose, multiple doses, e.g. two to six times per day, or by intravenous infusion for any selected duration. For example, in the case of a 75kg mammal, the dose range could be about 75 to 500mg per day, and it is expected that a typical dose would commonly be about 100mg per day. If discrete multiple doses are indicated, treatment might typically be 50mg of the compound of formula (I), given 4 times per day in the form of a tablet, capsule, liquid (e.g. syrup) or injection.

While it may be possible for the compounds of formula (I) to be administered alone as the raw chemical, it is preferable to present the compounds as a pharmaceutical formulation. Formulations of the present invention, for medical use, will generally comprise the compound of formula (I) together with one or more pharmaceutically acceptable carriers and, optionally, any other therapeutic ingredients. The carrier(s) must be pharmaceutically acceptable in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The present invention therefore further provides a pharmaceutical formulation comprising a compound of formula (I) together with a pharmaceutically acceptable carrier thereof.

The possible formulations include those suitable for oral, rectal, topical and parenteral (including sub-cutaneous, intramuscular and intravenous) administration or for administration to the lung or another absorptive site such as the nasal passages.

The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy.

All methods include generally the step of bringing the compound of formula (I) into association with a carrier which constitutes one or more accessory ingredients. Usually, the formulations are prepared by uniformly and intimately bringing the compound of formula (I) into association with a liquid carrier or with a finely divided solid carrier or with both and then, if necessary, shaping the product into desired formulations.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets, tablets or lozenges, each containing a predetermined amount of the compound of formula (I); as a powder or granules; or a suspension in an aqueous liquid or non-aqueous liquid such as a syrup, an elixir, an emulsion or a draught. The compound of formula (I) may also be presented as a bolus, electuary or paste.

A tablet may be made by compression or moulding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing, in a suitable machine, the compound of formula (I) in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active or dispersing agent. Moulded tablets may be made by moulding, in a suitable machine, a mixture of the powdered compound of formula (I) with any suitable carrier.

A syrup may be made by adding the compound of formula (I) to a concentrated, aqueous solution of a sugar, for example sucrose, to which may be added any accessory ingredient. Such accessory ingredient(s) may include flavourings, an agent to retard crystallisation of the sugar or an agent to increase the solubility of any other ingredient, such as a polyhydric alcohol for example glycerol or sorbitol.

Formulations for rectal administration may be presented as a suppository with a usual carrier such as cocoa butter.

Formulations suitable for parental administration conveniently comprise a sterile aqueous preparation of the compound of formula (I) which is preferably isotonic with the blood of the recipient.

In addition to the aforementioned ingredients, formulations of this invention, for example ointments, creams and the like, may include one or more accessory ingredient(s) for example a diluent, buffer, flavouring agent, binder, surface active agent, thickener, lubricant and/or a preservative (including an antioxidant).

From another aspect, the invention thus also comprises use of a compound of formula (I) for the manufacture of a medical preparation for use in the treatment of cancer.

EXAMPLES

The preparation of a number of particular compounds which are considered to be of especial interest for use as active therapeutic substances to inhibit proliferation of at least certain cancer cells and which provide examples of preferred embodiments of the invention (or examples of reference compounds for comparison purposes) will now be described in more detail, together with some general procedures for specific types of reactions. The compound references codes used elsewhere in this description are also quoted where applicable. It should be understood, however, that these specific examples are not intended to be construed in any way as limiting the scope of the invention.

EXAMPLE 1

4-Fluoro-2-(4-amino-3-methylphenyl)benzothiazole (Ia)

3-Methyl-4-nitrobenzoyl chloride (0.2 mol) was added slowly to a solution of 2-fluoroaniline (0.2 mol) in pyridine (100 ml). The resulting solution was heated under reflux for 60 min, then poured into water (300 ml). The precipitate was filtered from solution, washed with water (100 ml), followed by methanol to afford a white solid.

Lawesson's reagent (0.07 mol) was added to a solution of the benzanilide obtained (0.1 mol) in HMPA (50 ml). The resulting solution was heated at 100°C for 15 hr, then poured into water (300 ml). The product was extracted into diethyl ether (3 x 300 ml) and washed with water (3 x 200 ml). Evaporation of the solvent followed by recrystallization from methanol gave a bright orange solid.

A solution of the fluoro substituted thiobenzanilide thus obtained (0.2 mol) in aqueous sodium hydroxide (1.8 mol in 50 ml water) containing ethanol (5 ml) was added dropwise to a solution of potassium ferricyanide (0.8 mol) in water

(20 ml) at 90°C over a period of 60 min. The resulting solution was stirred at 90°C for a further 2 hr, then cooled in ice. The precipitate was filtered from solution and washed with water (100 ml). The product was purified by column chromatography (30% hexane/chloroform) to leave a bright yellow solid.

The product of the previous step (0.03 mol) and tin(II) chloride dihydrate (0.15 mol) were suspended in ethanol (150 ml) and heated under reflux for 2 hrs. The solvent was removed under vacuum and the resulting oil taken up in ethyl acetate (700 ml). The organic layer was washed with 2 M sodium hydroxide (2 x 200 ml), water (100 ml) and salt brine (30 ml). Removal of the solvent under vacuum followed by recrystallization from methanol gave the title compound as a pale yellow solid.

mp 203-205°C; IR 3491, 3369 (NH_2), 1624 (C=N) cm^{-1}; ^1H NMR (DMSO-d6) δ 7.86 (1H, dd, *J* 1.5, 8.5Hz, H-7), 7.71 (1H, d, *J* 2Hz, H-2'), 7.66 (1H, dd, *J* 2, 8.25Hz, H-6'), 7.37-7.30 (2H, m, H-5, H-6), 6.73 (1H, d, *J* 8.25, H-5'), 5.78 (2H, brs, NH_2), 2.17 (3H, s, CH_3); MS (CI) *m/z* 259.5 (M+1); Anal ($C_{14}H_{11}N_2SF$) C, H, N.

EXAMPLE 2

6-Fluoro-2-(4-amino-3-methylphenyl)benzothiazole (Ib)

The method of Example 1 was carried out using 4-fluoroaniline instead of 2-fluoroaniline. The title compound was obtained as a pale yellow solid.

mp 203-205°C; IR 3467, 3306 (NH_2), 1604 (C=N) cm^{-1}.

EXAMPLE 3

4-Fluoro-2-(4-aminophenyl)benzothiazole (Ic)

The method of Example 1 was carried out using 4-nitrobenzoyl chloride instead of 3-methyl-4-nitrobenzoyl chloride. The title compound was obtained as a pale yellow solid.

mp 219-221°C; IR 3456, 3350 (NH_2), 1604 (C=N) cm^{-1}.

EXAMPLE 4

6-Fluoro-2-(4-aminophenyl)benzothiazole (Id)

The method of Example 1 was carried out using 4-nitrobenzoyl chloride instead of 3-methyl-4-nitrobenzoyl chloride and 4-fluoroaniline instead of 2-fluoroaniline. The title compound was obtained as a pale yellow solid.

mp 152-155°C; IR 3333, 3219 (NH_2), 1604 (C=N) cm^{-1}.

EXAMPLE 5

4,5-Difluoro-2-(4-amino-3-methylphenyl)benzothiazole (Ie)

The method of Example 1 was carried out 2,3-difluoroaniline instead of 2-fluoroaniline. The title compound was obtained as a pale yellow solid.

mp 204-205°C; IR 3466, 3387 (NH_2), 1616 (C=N) cm^{-1}.

EXAMPLE 6

4,6-Difluoro-2-(4-amino-3-methylphenyl)benzothiazole (If)

The method of Example 1 was carried out using 2,4-difluoroaniline instead of 2-fluoroaniline. The title compound was obtained as a pale yellow solid.

mp 197-199°C; IR 3475, 3385 (NH_2), 1622 (C=N) cm^{-1}.

EXAMPLE 7

5,7-Difluoro-2-(4-amino-3-methylphenyl)benzothiazole (Ig)

The method of Example 1 was carried out using 3,5-fluoroaniline instead of 2-fluoroaniline. The title compound was obtained as a pale yellow solid.

mp 201-203°C; IR 3483, 3323 (NH_2), 1616 (C=N) cm^{-1}.

EXAMPLE 8

7-Fluoro-2-(4-amino-3-methylphenyl)benzothiazole (Ih)

3-Methyl-4-nitrobenzoyl chloride (0.2 mol) was added slowly to a solution of 2-bromo-3-fluoroaniline (0.2 mol) in pyridine (100 ml). The resulting solution was heated under reflux for 60 min, then poured into water (300 ml). The precipitate was filtered from solution, washed with water (100 ml), followed by methanol to afford a white solid.

Lawesson's reagent (0.07 mol) was added to a solution of the benzanilide obtained (0.1 mol) in HMPA (50 ml). The resulting solution was heated at 100°C for 15 hr, then poured into water (300 ml). The product was extracted into diethyl ether (3 x 300 ml) and washed with water (3 x 200 ml). Evaporation of the solvent followed by recrystallization from methanol gave a bright orange solid.

Sodium hydride (0.22 mol) was slowly added to a solution of the fluoro substituted thiobenzanilide thus obtained (0.2 mol) in N-methyl-2-pyrrolidinone (2 mol) at room temperature with stirring. The mixture was heated at 150°C for one hour then allowed to cool. Water (50ml) was then added and the precipitate collected by filtration and dried *in vacuo* to give the product as a white solid.

The product of the previous step (0.03 mol) and tin(II) chloride dihydrate (0.15 mol) were suspended in ethanol (150 ml) and heated under reflux for 2 hours. The solvent was removed under vacuum and the resulting oil taken up in ethyl acetate (700 ml). The organic layer was washed with 2 M sodium hydroxide (2 x 200 ml), water (100 ml) and salt brine (30 ml). Removal of the solvent under vacuum followed by recrystallization from methanol gave the title compound as a pale yellow solid.

mp 175-177°C; IR 3021, 1621 (C=N), 1470, 1215, 750 cm^{-1}.

EXAMPLE 9

5,6-Difluoro-2-(4-amino-3-methylphenyl)benzothiazole (Ii)

The method of Example 8 was carried out using 2-bromo-4,5-difluoroaniline instead of 2-bromo-3-fluoroaniline. The product was obtained as a pale yellow solid.

mp 226-228°C; IR 3497, 3333, 1632, 1466, 1454, 1406, 1314, 1142 cm^{-1}.

EXAMPLE 10

6,7-Difluoro-2-(4-amino-3-methylphenyl)benzothiazole (Ij)

The method of Example 8 was carried out using 2-bromo-5,6-difluoroaniline instead of 2-bromo-3-fluoroaniline.

EXAMPLE 11

5-Fluoro-2-(4-amino-3-methylphenyl)benzothiazole (Ik)

2-Amino-5-fluorobenzothiazole (5 g, 0.03 mol) was added to a solution of potassium hydroxide (25 g) in water (50 ml). The resulting mixture was heated under reflux for 5 hr, after which complete solution had occurred. After cooling, the reaction mixture was made acidic (pH 6) by the addition of acetic acid. A further portion of water (50 ml) was added and the resulting mixture stirred overnight. The solid precipitate was filtered from solution and recrystallized from ethanol/water to give bis-(2-amino-5-fluorophenyl)-disulphide as a pale yellow solid.

3-Methyl-4-nitrobenzoyl chloride (1.45 g, 7.3 mmol) was added to a solution of bis-(2-amino-5-fluorophenyl) disulfide (1 g, 3.65 mmol) in pyridine (10 ml). The resulting mixture was heated under reflux for 30 min, then poured into water (50 ml). The precipitate was filtered from solution, and washed with water (50 ml) to leave bis-[2-(3-methyl-4-nitrobenzanilide)-5-fluorophenyl] disulfide as a pale yellow solid.

To a solution of conc HCl (10 ml), ethanol (20 ml) and water (2 ml) was added bis-[2-(3-methyl-4-nitrobenzanilide)-5-fluorophenyl] disulfide (1 g, 1.6 mmol) and tin(II) chloride (1.86 g, 9.8 mmol). The reaction mixture was heated under reflux for 15 hr, cooled to 25°C and poured into water (75 ml). Sodium hydroxide (2 g) was added slowly, and the mixture stirred for 60 min. The precipitate was filtered from solution, and washed with water (10 ml) to leave a yellow solid which was purified by column chromatography (dichloromethane) followed by recrystallization from ethanol to give colorless needles.

mp 195-196°C; IR 3433, 3302 (NH_2), 1622 (C=N) cm^{-1}.

EXAMPLE 12

5-Fluoro-2-(4-aminophenyl)benzothiazole (II)

4-Nitrobenzoyl chloride (1.35 g, 7.3 mmol) was added to a solution of bis-(2-amino-5-fluorophenyl) disulfide prepared as described in Example 11 (1 g, 3.65 mmol) in pyridine (10 ml). The resulting mixture was heated under reflux for 30 min, then poured into water (50 ml). The precipitate was filtered from solution, and washed with water (50 ml) to leave bis-[2-(4-nitrobenzanilide)-5-fluorophenyl] disulfide as a pale yellow solid.

To a solution of conc HCl (10 ml), ethanol (10 ml) and water (2 ml) was added bis-[2-(4-nitrobenzanilide)-5-fluorophenyl] disulfide (1 g, 1.7 mmol) and tin(II) chloride (1 g, 5.2 mmol). The reaction mixture was heated under reflux for 15 hr, cooled to 25°C and poured into water (75 ml). Sodium hydroxide (2 g) was added slowly, and the mixture stirred for 60 min. The precipitate was filtered from solution, and washed with water (10 ml) to leave a yellow solid which was purified by column chromatography (dichloromethane) followed by recrystallization from ethanol to give colorless needles.

mp 153-155°C; IR 3460, 3290 (NH_2), 1637 (C=N) cm^{-1}.

EXAMPLE 13

4-Fluoro-2-(4-amino-3-iodophenyl)benzothiazole (Im)

A solution of the 4-fluoro-2-(4-aminophenyl)benzothiazole prepared as described in Example 3 (4.5 mmol) in acetic acid (20 ml) was added dropwise to a solution of iodine monochloride (5.8 mmol) in acetic acid (20 ml) at 25°C. The resulting solution was stirred for 2 hr, then the solvent was removed under vacuum. The residue was dissolved in chloroform (100 ml) and washed with aqueous sodium carbonate (50 ml), aqueous sodium thiosulfate (50 ml) and water (50 ml). Evaporation of the solvent, followed by column chromatography (chloroform) and recrystallization from methanol gave pale cream needles.

mp 210-211°C; IR 3474, 3377 (NH_2), 1610 (C=N) cm^{-1}.

EXAMPLE 14

5-Fluoro-2-(4-amino-3-iodophenyl)benzothiazole (In)

The method of Example 13 was carried out using the 5-fluoro-2-(4-aminophenyl)benzothiazole prepared as described in Example 12 instead of 4-fluoro-2-(4-aminophenyl) benzothiazole.

mp 187-188°C; IR 3447, 3317 (NH_2), 1612 (C=N) cm^{-1}.

EXAMPLE 15

6-Fluoro-2-(4-amino-3-iodophenyl)benzothiazole (Io)

The method of Example 13 was carried out using the 6-fluoro-2-(4-aminophenyl)benzothiazole prepared as described in Example 4 instead of 4-fluoro-2-(4-aminophenyl) benzothiazole.

mp 198-200°C; IR 3445, 3290 (NH_2), 1620 (C=N) cm^{-1}.

EXAMPLE 16

4-Fluoro-2-(4-amino-3-chlorophenyl)benzothiazole (Ip)

A solution of the 4-fluoro substituted 2-(4-amino-3-iodophenyl)benzothiazole prepared as described in Example 13 (1.35 mmol) and copper(I) chloride (6.75 mol) in DMF (5 ml) was heated under reflux overnight. After cooling, the reaction mixture was poured into ethyl acetate (100 ml), the precipitated solids were filtered off and the resulting solution evaporated to dryness. The product was purified by column chromatography (dichloromethane) followed by recrystallization from methanol to give a pale green solid.

mp 181-183°C; IR 3477, 3381 (NH_2), 1620 (C=N) cm^{-1}.

EXAMPLE 17

5-Fluoro-2-(4-amino-3-chlorophenyl)benzothiazole (Iq)

The method of Example 16 was carried out using the 5-fluoro substituted 2-(4-amino-3-iodophenyl)benzothiazole prepared as described in Example 14 instead of 4-fluoro substituted 2-(4-amino-3-iodophenyl)benzothiazole.

mp 177-178°C; IR 3481, 3369 (NH_2), 1631 (C=N) cm^{-1}.

EXAMPLE 18

6-Fluoro-2-(4-amino-3-chlorophenyl)benzothiazole (Ir)

The method of Example 16 was carried out using the 6-fluoro substituted 2-(4-amino-3-iodophenyl)benzothiazole prepared as described in Example 15 instead of 4-fluoro substituted 2-(4-amino-3-iodophenyl)benzothiazole.

mp 194-195°C; IR 3472, 3310 (NH_2), 1628 (C=N) cm^{-1}.

EXAMPLE 19

4-Fluoro-2-(4-amino-3-bromophenyl)benzothiazole (Is)

Bromine (0.8 mmol) was added to a solution of the 4-fluoro-2-(4-aminophenyl) benzothiazole prepared as described in Example 3 (0.8 mmol) in dichloromethane (20 ml) at 10°C. The resulting solution was stirred for 10 min, then poured into water/ice (10 ml). The organic layer was removed and washed

with 10% sodium thiosulfate (10 ml), water (10 ml) and evaporated. The product was purified by column chromatography (dichloromethane) to leave a white solid.

mp 211-213°C; IR 3416, 3379 (NH_2), 1618 (C=N) cm^{-1}.

EXAMPLE 20

5-Fluoro-2-(4-amino-3-bromophenyl)benzothiazole (It)

The method of Example 19 was carried out using the 5-fluoro-2-(4-aminophenyl) benzothiazole prepared as described in Example 12 instead of 4-fluoro-2-(4-aminophenyl) benzothiazole.

mp 181-183°C; IR 3464, 3311 (NH_2), 1612 (C=N) cm^{-1}.

EXAMPLE 21

6-Fluoro-2-(4-amino-3-bromophenyl)benzothiazole (Iu)

The method of Example 19 was carried out using the 6-fluoro-2-(4-aminophenyl) benzothiazole prepared as described in Example 4 instead of 4-fluoro-2-(4-aminophenyl) benzothiazole.

mp 209-211°C; IR 3462, 3300 (NH_2), 1626 (C=N) cm^{-1}.

EXAMPLE 22

2-(4-aminophenyl)benzothiazole alanine hydrochloride salt (Iv)

2-(4-aminophenyl)benzothiazole (7.75mmol) was dissolved in dichloromethane (100ml) and stirred at room temperature. To this solution was added 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride (2.3mmol), HOBt (2.3mmol) and Boc protected alanine (2.3mmol). After stirring for 24 hrs a further 2.3mmol of each reactant was added, and stirring continued for a further 24 hrs. This procedure was repeated twice more and stirring continued for a further 3 days, until a clear solution had occurred. The solvent was removed

under vacuum and the resulting oil purified by column chromatography (2% methanol/ dichloromethane). Recrystallisation from ethanol gave a white solid.

The Boc protected amino acid derivative thus obtained (3.5mmol) was dissolved in dichloromethane (20ml). Dry HCl gas was bubbled through the solution to saturate it, then the reaction mixture was stirred for a further 2 hrs at 25°C. The precipitate was filtered from solution and washed with dichloromethane (10ml), to leave a bright yellow crystalline solid.

mp 258-259°C; MS (AP) *m/z* 298 (M+1).

EXAMPLE 23

2-(4-amino-3-methylphenyl)benzothiazole alanine hydrochloride salt (Iw)

The title compound was prepared using the method of Example 22 but with 2-(4-amino-3-methylphenyl)benzothiazole instead of 2-(4-aminophenyl)-benzothiazole.

mp 272-274°C; MS (AP) *m/z* 312 (M+1).

EXAMPLE 24

2-(4-amino-3-chlorophenyl)benzothiazole alanine hydrochloride salt (Ix)

The title compound was prepared using the method of Example 22 but with 2-(4-amino-3-chlorophenyl)benzothiazole instead of 2-(4-aminophenyl)-benzothiazole.

mp 240-243°C; MS (AP) *m/z* 332 (M+1).

EXAMPLE 25

2-(4-aminophenyl)benzothiazole lysine hydrochloride salt (Iy)

The title compound was prepared using the method of Example 22 but with BOC protected lysine instead of BOC protected alanine.

mp 296-298°C; MS (AP) *m/z* 355 (M+1).

EXAMPLE 26

2-(4-amino-3-methylphenyl)benzothiazole lysine hydrochloride salt (Iz)

The title compound was prepared using the method of Example 22 but with 2-(4-amino-3-methylphenyl)benzothiazole instead of 2-(4-aminophenyl)benzothiazole and BOC protected lysine instead of BOC protected alanine.

mp 290-293°C; MS (AP) *m/z* 369 (M+1).

EXAMPLE 27

2-(4-amino-3-chlorophenyl)benzothiazole lysine hydrochloride salt (Iaa)

The title compound was prepared using the method of Example 22 but with 2-(4-amino-3-chlorophenyl)benzothiazole instead of 2-(4-aminophenyl)-benzothiazole and BOC protected lysine instead of BOC protected alanine.

mp 278-279°C; MS (AP) *m/z* 389 (M+1).

EXAMPLE 28

2-(4-amino-3-methylphenyl)benzothiazole serine hydrochloride salt (Iab)

The title compound was prepared using the method of Example 22 but with 2-(4-amino-3-methylphenyl)benzothiazole instead of 2-(4-aminophenyl)-benzothiazole and BOC protected serine instead of BOC protected alanine.

mp 265-269 °C; MS (CI) *m/z* 328 (M+1).

EXAMPLE 29

6-Fluoro-2-(4-amino-3-methylphenyl)benzothiazole alanine hydrochloride salt (Iac)

The title compound was prepared using the method of Example 22 but with 6-fluoro-2-(4-amino-3-methylphenyl)benzothiazole prepared as described in Example 2 instead of 2-(4-aminophenyl)-benzothiazole.

mp 282-285°C; MS (CI) *m/z* 330.3 (M+1).

EXAMPLE 30

5-Fluoro-2-(4-amino-3-methylphenyl)benzothiazole lysine hydrochloride salt (Iad)

The title compound was prepared using the method of Example 22 but with 5-fluoro-2-(4-amino-3-methylphenyl)benzothiazole prepared as described in Example 11 instead of 2-(4-aminophenyl)benzothiazole and BOC protected lysine instead of BOC protected alanine.

mp 290-294°C; MS (CI) *m/z* 387.4 (M+1).

EXAMPLE 31

6-Fluoro-2-(4-amino-3-methylphenyl)benzothiazole lysine hydrochloride salt (Iae)

The title compound was prepared using the method of Example 22 but with 6-fluoro-2-(4-amino-3-methylphenyl)benzothiazole prepared as described in Example 2 instead of 2-(4-aminophenyl)benzothiazole and BOC protected lysine instead of BOC protected alanine.

mp 298-303°C; MS (CI) *m/z* 387.2 (M+1).

EXAMPLE 32

5-Fluoro-2-(4-amino-3-methylphenyl)benzothiazole alanine hydrochloride salt (Iaf)

The title compound was prepared using the method of Example 22 but with 5-fluoro-2-(4-amino-3-methylphenyl)benzothiazole prepared as described in Example 11 instead of 2-(4-aminophenyl)benzothiazole.

mp 280-284°C; MS (CI) *m/z* 330.3 (M+1).

EXAMPLE 33

5-Fluoro-2-(4-amino-3-methylphenyl)benzothiazole leucine hydrochloride salt (Iag)

The title compound was prepared using the method of Example 22 but with 5-fluoro-2-(4-amino-3-methylphenyl)benzothiazole prepared as described in Example 11 instead of 2-(4-aminophenyl)benzothiazole and with BOC protected leucine instead of BOC protected alanine.

EXAMPLE 34

5-Fluoro-2-(4-amino-3-methylphenyl)benzothiazole phenylalanine hydrochloride salt (Iah)

The title compound was prepared using the method of Example 22 but with 5-fluoro-2-(4-amino-3-methylphenyl)benzothiazole prepared as described in Example 11 instead of 2-(4-aminophenyl)benzothiazole and with BOC protected phenylalanine instead of BOC protected alanine.

EXAMPLE 35

5-Fluoro-2-(4-amino-3-methylphenyl)benzothiazole glycine hydrochloride salt salt (Iai)

The title compound was prepared using the method of Example 22 but with 5-fluoro-2-(4-amino-3-methylphenyl)benzothiazole prepared as described in Example 11 instead of 2-(4-aminophenyl)benzothiazole and with BOC protected glycine instead of BOC protected alanine.

As will be seen, the invention presents a number of different aspects and it should be understood that it embraces within its scope all novel and inventive features and aspects herein disclosed, either explicitly or implicitly and either singly or in combination with one another. Also, many detail modifications are possible and, in particular, the scope of the invention is not to be construed as being limited by the illustrative example(s) or by the terms and expressions used herein merely in a descriptive or explanatory sense.